BMC Ophthalmology

RESEARCH

Open Access

Efficacy and safety of treat-and-extend intravitreal brolucizumab in naive and switched patients with macular neovascularization: one-year follow-up study

Francesco Faraldi[1,2], Carlo Alessandro Lavia[1,2*], Marco Nassisi[3,4], Raphael Kilian[5], Clara Rizzo[5], Maria Cristina Savastano[6,7], Stanislao Rizzo[6,7,8,9], Fabrizio Giansanti[10,11] and Daniela Bacherini[10,11]

Abstract

Background to analyze, at one year, the efficacy and safety of treat-and-extend (T&E) intravitreal (IV) Brolucizumab in patients affected by macular neovascularization (MNV). Both naïve and previously treated (i.e., switched) patients were included, and the data from the two groups were compared.

Methods anatomical (i.e., central subfoveal thickness, CST; presence of fluid), functional (i.e., best corrected visual acuity, BCVA) and treatment-related (i.e., number of IV injections within the study period; number of patients reaching a 12-weeks interval between treatments) data from 41 eyes of 41 subjects (20 naïve and 21 switched) were analyzed. Patients were treated with 3 monthly IV injections followed by a T&E regimen based on a disease activity assessment performed at each scheduled IV treatment.

Results significant CST reduction (from 412.1 ± 115.8 to 273.2 ± 61.6; $p < 0.05$) and BCVA (mean; p) improvement were observed in the naïve group, while in the switched cohort, both parameters were almost stable. In the naïve and switched groups, 55% and 33.5% of patients, respectively, reached a 12-week IV interval at one year, with a mean of 6.55 ± 1 and 7.43 ± 0.68 IV treatments, respectively. One patient with mild anterior uveitis without sequelae was recorded.

Conclusion In patients with MNV, IV Brolucizumab injections following a T&E regimen demonstrated great efficacy and a good safety profile, with greater anatomical and functional results in naïve patients.

Trial registration This study was approved by the Local Ethics Committee (protocol number 155/2020, general registry number n°11486, InterHospital Ethics Committee, San Luigi Gonzaga Hospital, Orbassano, Italy).

Keywords Intravitreal Brolucizumab, Macular neovascularization, Treat and extend, Naïve patients, Switched patients, Intravitreal injection interval, OCT, Brolucizumab safety

*Correspondence:
Carlo Alessandro Lavia
carlo.lavia@gmail.com

Full list of author information is available at the end of the article

Background

Age-related macular degeneration (AMD) is a leading cause of visual impairment in developed countries, and the management of its neovascular stage is becoming a significant challenge for health care providers due to the frequent treatments and follow-up needed for a constantly increasing number of patients [1, 2].

Intravitreal injections (IVs) have significantly changed the natural course of macular neovascularization (MNV), and their efficacy has become even more evident due to earlier diagnosis and treatment and the adoption of more effective treatment regimens [3–5].

Indeed, significant efforts have been made to obtain the best functional and anatomical results with the lowest number of IV injections and follow-up evaluations. Treatment regimens such as "treat and extend" (T&E) are therefore currently widely used, providing results that are similar to those obtained with fixed regimens with fewer IV injections per year [6, 7]. In this context, newer drugs such as Brolucizumab and Faricimab seem promising for achieving good control of disease activity with fewer treatments [8, 9]. Brolucizumab has demonstrated excellent efficacy in retinal fluid control in several MNV subtypes and in both treatment-naïve and previously treated lesions [10–14]. However, the initial enthusiasm for this new drug has somewhat faded due to the increasing number of reports on adverse intraocular events following its use, from mild inflammatory reactions to severe retinal vascular occlusive events [15, 16]. In this context, due to the relatively low number of real-life reports on the use of Brolucizumab, we aimed to report one-year anatomical and functional data on its use in both naïve and previously treated patients affected by MNV and compare the results from the two groups.

Methods

This study, conducted in the Ophthalmology Department, ASL TO5, Turin, Italy, was approved by the Local Ethics Committee (protocol number 155/2020, general registry number n°11486, Inter-Hospital Ethics Committee, San Luigi Gonzaga Hospital, Orbassano, Italy) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

We retrospectively studied consecutive patients who underwent intravenous Brolucizumab (IV) injections and who were followed up for 1 year between July 2020 and March 2023.

The inclusion criteria were as follows: patients affected by active MNV secondary to AMD involving the central subfield (circular area within 1 mm diameter around the foveal center as assessed by SD-OCT) treated with IV Brolucizumab; 1-year (52±4 weeks) follow-up availability since the first Brolucizumab IV injection ; patients whose clinical and imaging data were available (SD-OCT cube at baseline and at each visit with follow-up mode, best corrected visual acuity; complete ophthalmic examination) at baseline and at each follow-up visit; and patients whose best corrected visual acuity (BCVA) was ≥20/400 at baseline. Patients included in the study could be either treatment naïve (i.e., naïve group) or previously treated with other anti-VEGF drugs and subsequently switched to Brolucizumab (i.e., switch group).

The exclusion criteria were the presence of MNV other than age-related MNV; the presence of other significant ocular diseases that could interfere with data acquisition (e.g., dense cataract, vitreous asteroid hyalosis) or that could significantly alter data reliability (e.g., advanced glaucoma or the presence of concomitant diabetic retinopathy); and a history of previous retinal or macular surgery in the study eye.

Patients' examination

All patients underwent a complete ophthalmic examination at baseline and at each follow-up visit, including best corrected visual acuity (BCVA, reported in Snellen and converted in logMAR) testing; slit-lamp examination with anterior segment and dilated fundus examination; Goldmann applanation tonometry; OCT; OCT-Angiography (OCT-A) examination; fundus autofluorescence; and, when deemed necessary, fluorescein angiography and indocyanine green angiography.

OCT-OCTA was performed using a Heidelberg Spectrialis HRA+OCT device (Heidelberg Eye Explorer, Version 1.11.2.0; Software V7.0.1; Heidelberg Engineering, Germany).

In all subjects, a horizontal raster acquisition of ≈20×20° centered on the fovea, composed of 97 parallel B-scans, was acquired at baseline and at each follow-up visit. Adjunctive scans were performed in areas of interest when deemed necessary.

OCTA acquisition was performed using ≈20×20° high-speed acquisition centered on the fovea and composed of 512 sections.

After checking for correct retinal layer segmentation, retinal thickness in the central mm was automatically obtained from the raster pattern and used for analysis in all subjects.

OCT and OCTA follow-up modes were employed for all visits following the baseline acquisition.

Disease activity assessment was performed on the basis of BCVA and structural OCT.

The following structural OCT findings were considered:

- Intraretinal fluid (IRF) is defined as intraretinal hyporeflectivity within the retina (with the exception of outer retinal tabulations).

- Subretinal fluid (SRF) is defined as hyporeflective space between the photoreceptor outer segment tips and the retinal pigment epithelium (RPE).
- Sub-RPE fluid, defined as hyporeflective space between the elevated retinal pigment epithelium and Bruch's membrane.
- Subretinal hyperreflective material (SHRM) is defined as hyperreflective material located external to the retina and internal to the RPE.

Fluid assessment was performed on presence or absence (i.e., it was not a quantitative assessment) and was used to assess MNV activity and plan the IV injections.

TREATMENT PLANNING: treat and extend regimen.

All patients were treated with a loading dose of IV Brolucizumab at weeks 0, 4, and 8. On the day of the third injection (i.e., week 8), on the basis of the disease activity assessment, subsequent treatment at 8 or 12 weeks was established. After the loading phase, the disease activity assessment was performed at all scheduled IV injections following a traditional T&E regimen [17, 18].

OCT-based disease activity assessment could result in three different scenarios: (1) no MNV activity (i.e., no fluid detected on OCT); (2) decreased MNV activity; and (3) stable or increased MNV activity.

In the case of no MNV activity detected, the following treatment was planned at +4 weeks in relation to the current inter-IV injection interval (e.g., a current IV injection at week 8 implied a subsequent IV injection at week 12). In selected cases (e.g., when a previous interval increase resulted in MNV reactivation), +2 weeks was used instead of +4.

In the case of decreased MNV activity, the following treatment was planned at the current inter-IV injection interval (e.g., a current IV injection at week 8 implied a subsequent IV injection at week 8).

In the case of stable or increased MNV activity, the following treatment was planned at a shorter inter-IV injection interval (e.g., a current IV injection at week 12 implied a subsequent IV injection at week 8).

When a BCVA decrease ≥ 0.1 logMAR compared to the baseline value (or to previous assessment) was observed and was supported by OCT-based disease activity, the IV injection interval was reduced.

When the IV injection interval eventually reached 16 weeks without signs of MNV activity or BCVA loss, the clinician could choose between performing a further IV injection at 20 weeks or switching to a pro re nata (PRN) regimen, based on clinical signs and patient history.

Safety assessment

Due to the greater incidence of different entities of intraocular inflammation reported following IV Brolucizumab injections compared to other routinely used anti-VEGF agents, great attention has been given at enrollment (female patients, a history of previous intraocular inflammation or retinal vascular occlusion were considered at higher risk, and if deemed necessary, another anti-VEGF agent was proposed) and in the evaluation of adverse events.

Before treatment initiation, patients were informed about possible adverse events, and once the treatment began, they were instructed on the symptoms suggestive of intraocular inflammation (e.g., floaters, blurred or decreased vision). Moreover, after each IV injection during the loading phase and on a voluntary basis during further treatments, patients were recalled to our clinic to perform a safety assessment (complete ophthalmic examination and OCT scans).

Statistical analysis

Continuous variables were checked for normality using the Shapiro–Wilk test. A parametric t test or a nonparametric Mann–Whitney test was used when necessary to compare the variables between groups. Statistical analysis was performed using IBM SPSS Statistics (SPSS Statistics, version 19.0, Chicago, IL, USA). Binary variables were arranged in cross-correlation tables and analyzed using the chi-squared test.

The results are presented as the mean ± standard deviation (SD) or as the median with range for continuous variables and as proportions (%) for categorical variables. P values < 0.05 were considered to indicate statistical significance.

Results

Among the 64 eyes of 60 patients treated with Brolucizumab during the study period, 41 eyes from 41 patients met the inclusion criteria: 20 patients were treatment naïve (naïve cohort), while 21 were previously treated with other anti-VEGF drugs (9 with aflibercept, 43%; 2 with ranibizumab, 9.5%; 10 with both aflibercept and ranibizumab, 47.5%; switch cohort). In the switch cohort, patients underwent a mean of 12.14 ± 3.76 IV injections over a mean period of 22.62 ± 8.27 months.

The reasons for the switch from other anti-VEGF drugs were fluid persistence or increase despite multiple closed-range treatments (Q4w regimen in 9 eyes, accounting for 43%, and Q6w regimen in 12 eyes, accounting for 57%) and/or documented MNV recurrence when the treatment was extended.

The demographic and baseline structural and functional data are presented in Table 1.

The loading phase of three-month injections was performed in all patients. At the one-year follow-up, naïve patients underwent a mean of 6.55 ± 1 IV injections, and 55% of them achieved a q12w regimen. The switch cohort presented a greater mean number of IV injections

Table 1 Demographic and baseline data

	N	Age (years)	Gender *n* (%)	Baseline BCVA (logMAR)	Baseline CST (µm)	Baseline fluid (IR; SR; sub-RPE)
All patients	41	78.41 ± 6.99	M = 25 (61%)	0.36 ± 0.24	369.2 ± 101.8	48.5%; 97.5%; 85%
Naïve cohort	20	80.35 ± 5.71	M = 12 (60%)	0.44 ± 0.25	412.1 ± 115.8	70%; 95%; 85%
Switch cohort	21	76.57 ± 7.72	M = 13 (62%)	0.28 ± 0.19	328.4 ± 66.5	28.5%; 100%; 85.5%

N: number; M: male; BCVA: best corrected visual acuity; CST: central subfoveal thickness; IR: intraretinal; SR: subretinal; RPE: retinal pigment epithelium. The values are expressed as the means ± standard deviations

Table 2 Treatment, functional and anatomical data at 1-year follow-up

	Mean (SD) *n* of IV injections	Q12w regimen at final follow up (*N*, %)	Final BCVA (difference vs. baseline: *p*)	Final CST (difference vs. baseline: *p*)	Final fluid (IR; SR; sub-RPE)
Naïve cohort	6.55 ± 1	11; 55%	0.29 ± 0.21 ($p < 0.05$)	273.2 ± 61.6 ($p < 0.05$)	20%; 20%; 35%
Switch cohort	7.43 ± 0.68	7; 33.5%	0.26 ± 0.18 (p: 0.38)	314.8 ± 58.7 (p: 0.25)	28.5%; 38%; 43%

IV: intravitreal; Q12w: 12-week interval between IV injections; BCVA: best corrected visual acuity; CST: central subfoveal thickness; IR: intraretinal; SR: subretinal; RPE: retinal pigment epithelium. The values are expressed as percentages or means ± standard deviations

per year, at 7.43 ± 0.68, with 33.5% of patients receiving a q12w regimen ($p = 0.002$).

After 1 year, the mean BCVA significantly improved in naïve patients, from 0.44 logMAR (20/51 Snellen equivalent) to 0.29 logMAR (20/39). However, no significant differences were observed in the switch group, where BCVA remained stable over time, from 0.28 to 0.26 logMAR (20/39 Snellen equivalent).

At the final follow-up, in the naïve cohort, 55% of patients presented an improvement in BCVA, with 30% of patients who gained more than 0.2 logMAR. The remaining 45% of patients ($n = 9$) presented a stable BCVA over time (mean BCVA 0.36 ± 0.17). In the switch cohort, 33% of patients gained between 0.1 and 0.2 logMAR, while 57% of patients remained unchanged (mean BCVA 0.26 ± 0.20); two patients experienced VA loss (0.1 and 0.3 logMAR).

The structural, functional and IV injection data are presented in Table 2.

Structural OCT scans from six patients included in the naïve and switch cohorts are presented in Figs. 1 and 2, respectively. The complete history of a patient from the switch cohort is presented in Fig. 3.

Inflammatory adverse events were observed in 1 patient in the naïve group who presented with conjunctivitis associated with mild anterior uveitis that completely resolved after topical steroids. The event occurred during the loading phase; the patient was strictly followed-up, and no recurrences were observed during the subsequent IV Brolucizumab injections. Finally, one patient in the switch group developed a large RPE tear during treatment that was responsible for VA loss (from 20/32 at baseline to 20/63 at last follow-up); this patient is currently receiving Q8w Brolucizumab treatment.

Discussion

In this study, we report one-year follow-up results for patients treated with the T&E regimen of IV Brolucizumab who were both naïve (i.e., naïve cohort) or previously treated with other IV anti-VEGF agents (i.e., switch cohort).

Our results showed that significant BCVA improvement and fluid reabsorption were achieved in all patients, with greater functional and anatomic results in the naïve cohort, with 30% of patients gaining more than 0.2 logMAR (i.e., 2 ETDRS chart lines).

Since the advent of OCT technology, the presence of fluids (IR, SR or sub-RPE) has become a milestone in MNV activity assessment. Indeed, a positive correlation between the presence of fluids and retinal thickness and visual function has been widely reported [19, 20].

More recently, particular attention has been given to retinal fluid fluctuations, which present even greater accuracy in predicting visual prognosis [21, 22]. Several studies suggest that poor fluid control over time is associated with a poor visual prognosis in the mid- and long-term, and this is particularly evident for patients with IRF [23]. Indeed, intraretinal fluid, which can be of both exudative and degenerative origin, is often associated with permanent damage to the neurosensory retina, leading to a greater incidence of atrophy and fibrosis [24–26]. On the other hand, the management and tolerance of SRF are still debated, with some studies even advocating a protective role of some SRF and others underlining the importance of strict fluid control [26, 27].

Since its introduction, Brolucizumab has demonstrated great efficacy in fluid reabsorption, with promising data for different MNV subtypes from several series.

In the Hawk and Harrier studies, naïve patients affected by type 1 and type 2 MNV were randomized

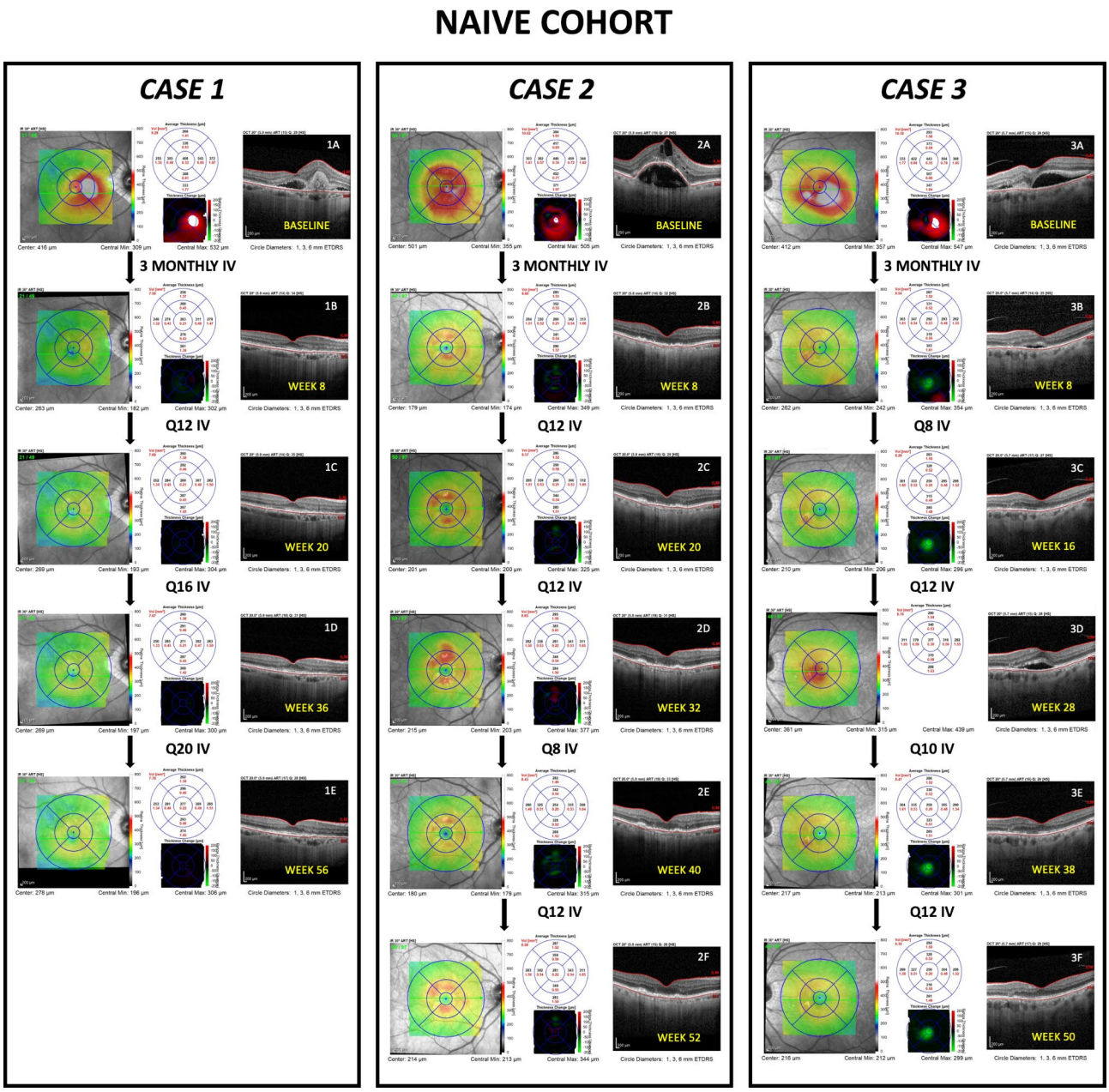

Fig. 1 One-year follow-up of three naïve patients treated with Brolucizumab following a Treat-and-Extend regimen. Boxes named: "case 1", "case 2" and "case 3". Panel **A** represents the baseline and panels **B** to E/F represent each follow-up assessment; the week of each assessment is reported in yellow at the bottom of each OCT structural B-Scan (on the right, at the bottom). At each assessment, the IV injection interval was established (reported between each figure, next to the black arrow). Example, Patient 1: 1 A: baseline infrared fundus image with a color-coded thickness map overlay (on the left); sectorial thickness map (in the center, top), retinal thickness change map (in the center, bottom) and structural OCT B-scan passing through the center showing an MNV with SHRM and abundant SR fluid. 1B: On the day of the third IV injection (third of three monthly IV injections of the loading phase), at week 8, no MNV activity was detected, and the following treatment was planned at 12 weeks (i.e., q12). 1 C: At week 20, no MNV activity was detected, and the following IV injection was planned at q16. 1D: At week 36, no MNV activity was detected, and the following IV injection was planned at q20. 1E: At week 56, at the end of the follow-up (i.e., 52 ± 4 weeks), no MNV activity was detected

to receive either Brolucizumab or Aflibercept and followed up for 48 weeks. Patients receiving Brolucizumab were treated every 8 or 12 weeks on the basis of a disease activity assessment. The studies reported a mean BCVA gain between 6.6 and 6.9 letters (cohort treated with 6 mg of Brolucizumab) and a mean central subfoveal thickness (CST) reduction between 172.8 and 193.8 µm. Overall, between 51% and 56% of patients were maintained on q12w dosing at 48 weeks [9]. At 96 weeks, the trials showed a VA gain between 5.9 and 6.1 letters

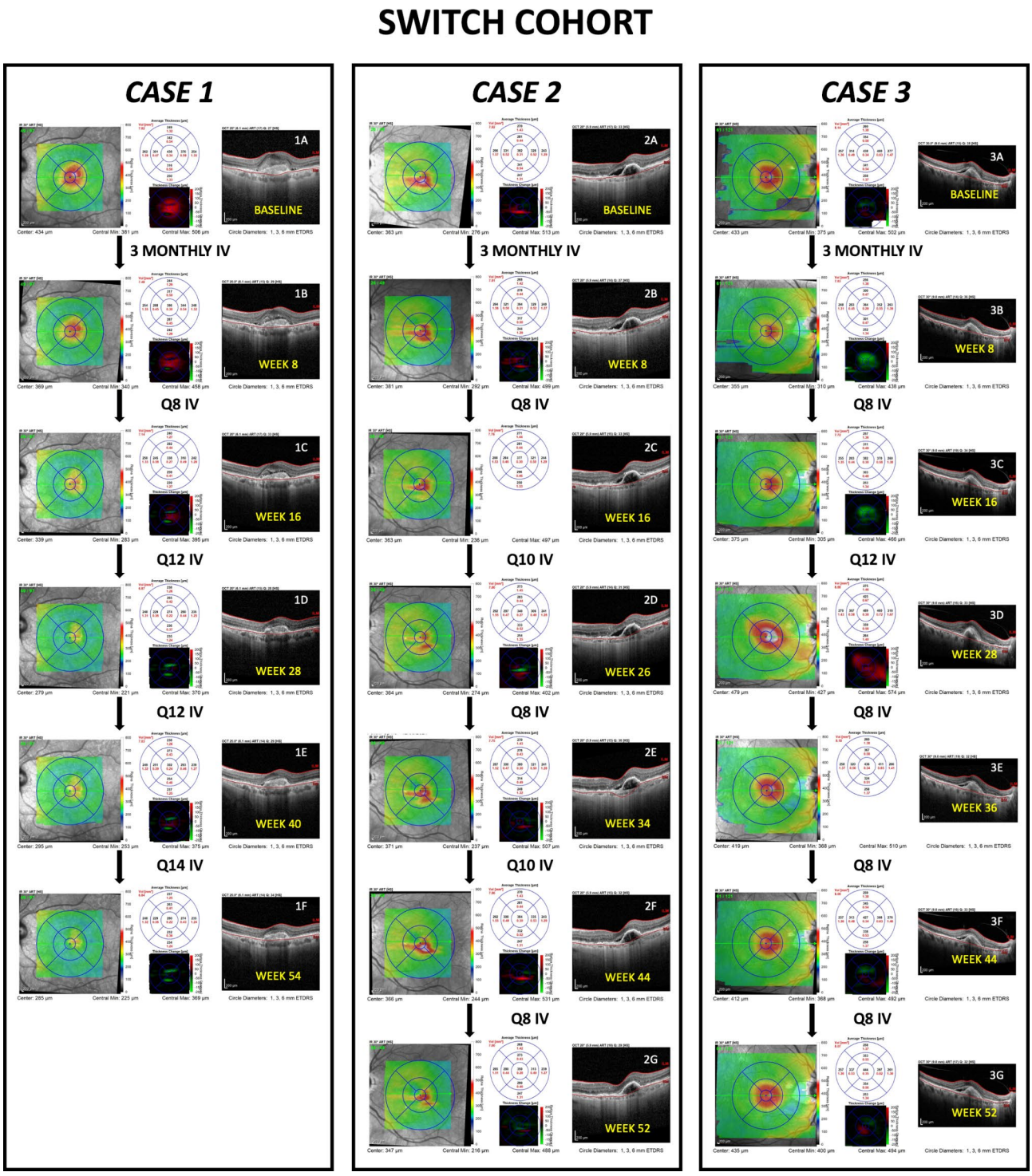

Fig. 2 One-year follow-up of three switch patients treated with Brolucizumab following a treat-and-extend regimen. Boxes named "case 1", "case 2" and "case 3". Panel A represents the baseline and panels B to F/G represent each follow-up assessment; the week of each assessment is reported in yellow at the bottom of each OCT structural B-Scan. At each assessment, the IV injection interval was established (reported between each figure, next to the black arrow)

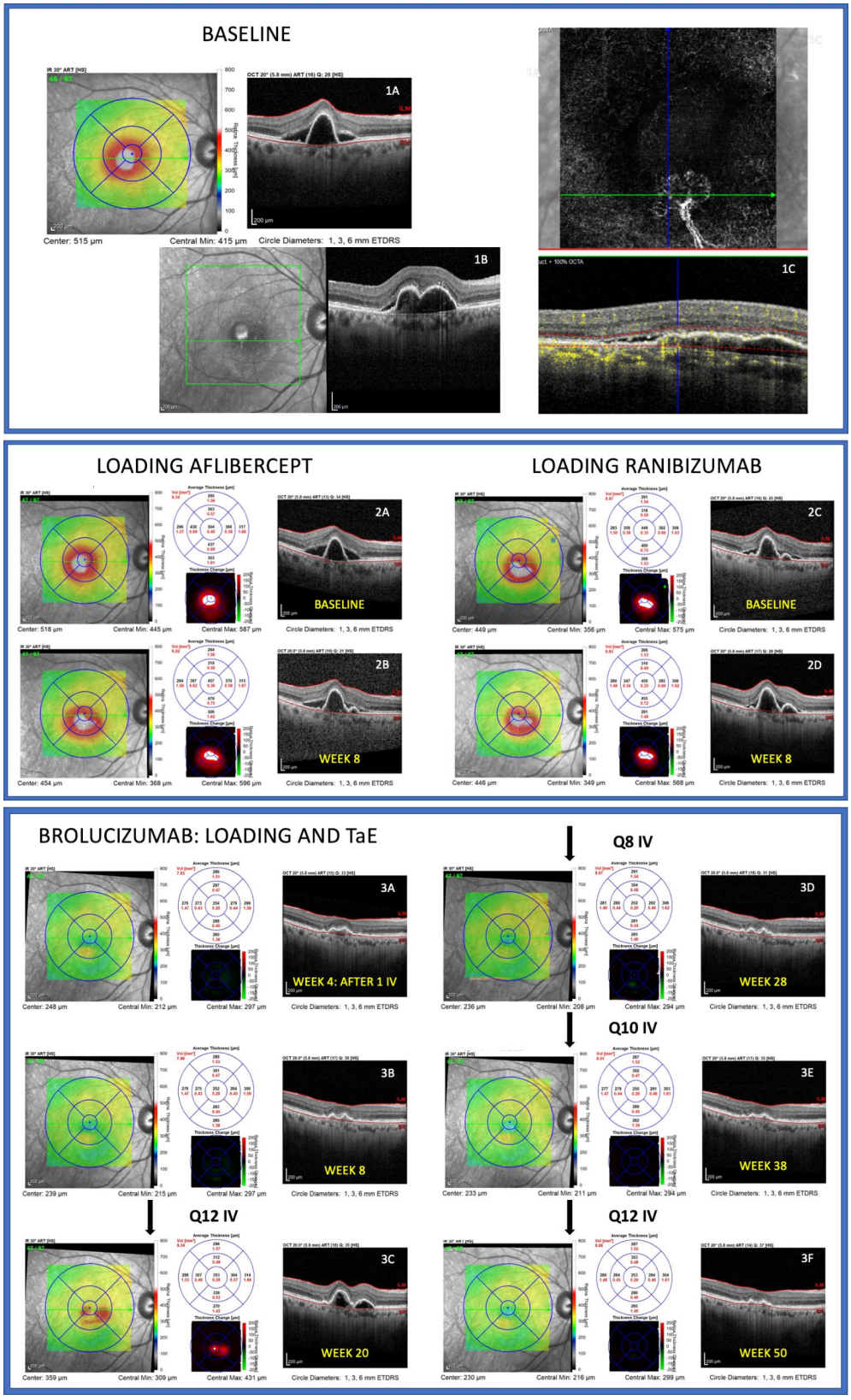

Fig. 3 (See legend on next page.)

(See figure on previous page.)

Fig. 3 Complete history of a patient from the switch cohort. In the first box (1, top), the baseline structural OCT and OCT-A features are reported: the patient presented with polypoidal choroidal vasculopathy (PCV), with subretinal and sub-retinal pigment epithelium (RPE) fluid at baseline. In the second box (2, middle), the baseline (top) and postloading phase (i.e., 4 weeks after the third IV injection, bottom) of structural OCT are reported; in the left column, the OCT performed during treatment with Aflibercept is shown, and in the left column, the OCT performed during treatment with Ranibizumab is shown. In both cases, due to anatomical unresponsiveness accompanied by functional decay (BCVA 20/32 at baseline decreased to 20/40 at the end of the loading phase with both anti-VEGF drugs), a switch was proposed after three monthly IV injections. The third box (3, bottom) represents the one-year follow-up with Brolucizumab, from Fig. 3A, at week 4 (i.e., the day of the second IV injection) to Fig. 3F, at week 50. Notably, due to a complete response at week 8 (Fig. 3B), further IV injection was planned at q12, but recurrence occurred at week 20 (Fig. 3C); a q12 regimen with no fluid was finally achieved at the last IV injection at week 50 (Fig. 3F)

(6 mg of Brolucizumab), a mean CST reduction between 174.8 and 197.7 μm, and q12w dosing in 38.6–45.4% of the eyes (at week 92) [28]. A 96-week subanalysis of a cohort of patients with residual fluid at weeks 4 to 12 (i.e., early residual fluid), reported greater results achieved with Brolucizumab as compared to Aflibercept, providing a mean VA gain of 6.4 letters and a CST reduction of 202 μm [29].

In a 2-year real-life study on naïve patients with type 1 MNV treated with Brolucizumab using a T&E regimen, Matsumoto et al. reported a significant improvement in BCVA from baseline to week 96, with an average IV injection interval of 14±3.3 weeks [30]. In their study, patients underwent a mean of 6.4±0.6 IV injections in the first year, which is similar to our data (6.55±1).

In a 1-year real-life study on refractory MNV previously treated with a mean of 36±22 IV injections, Abdin et al. observed an almost unchanged VA (from 51±16 to 50±19 letters) and a CST reduction from 374±158 μm to 298±92 μm [31]. Patients underwent a mean of 6.4±0.9 IV injections in the study period, which is lower than the 7.43±0.68 that we observed in the current study.

In our series, 55% of naïve patients presented no signs of MNV activity at 12-week intervals, meaning that, in the presence of disease stability over time, they could receive up to four IV injections per year from the second year of treatment.

In the switch cohort, a significantly lower percentage of patients presented no MNV activity at longer intervals, with 33.5% of them reaching q12w. The lower proportion of patients who achieved a q12w regimen in the switch cohort might be related to intrinsic features of the disease that led to a poor or incomplete response to anti-VEGF drugs. On the other hand, these patients never reached a q12w interval with other anti-VEGF agents underlying the greater drying effect of Brolucizumab, which might have been particularly effective in our cohort of patients previously treated on a q4 or q6 basis. Indeed, in a large study by MacCumber et al. on patients who switched to Brolucizumab, greater results in terms of visual gain and IV injection extension were observed in those patients with shorter IV injection intervals and a history of anti-VEGF therapy before switching [32].

In terms of anatomical and functional results, consistent differences emerged between the two cohorts. In the naïve group, we observed a significant improvement in BCVA accompanied by a decrease in the CST, while in the switch cohort, both parameters were almost unchanged within the period. To correctly interpret this finding, we should consider that the typical functional and anatomical improvements were likely achieved after the treatments were performed at their naïve status.

Adverse events after IV Brolucizumab injections have been widely documented in recent years, ranging from mild intraocular inflammation to severe vasculitis, and several papers have reported useful information on the definition of the risk of adverse events and on its management [33, 34]. Fonollosa et al. distinguished several steps in the selection and management of patients: profiling (risk factors and risk-benefit evaluation), choosing the treatment regimen, monitoring and immediate treatment in cases of intraocular inflammation [35]. Recently, Mora et al. reported a case of contralateral retinal changes in a patient affected by bilateral MNV treated with Brolucizumab in the right eye: after two consecutive Brolucizumab IVI, the CMT remarkably decreased in both eyes. To explain this finding, the authors postulated a "molecular escape" of the drug that, presenting a particularly low molecular weight, could more easily reach the contralateral eye [36].

In our study, particular attention was given at enrollment (female patients, a history of previous intraocular inflammation or retinal vascular occlusion were considered at higher risk, and if deemed necessary, another anti-VEGF agent was proposed), and in the evaluation of adverse events, patients were carefully monitored with enforced follow-up visits during the loading phase and then instructed to detect those symptoms that were suggestive of intraocular inflammation or retinal vascular events. At one year, we did not observe significant adverse events, and if we extend our analysis to the whole cohort of patients treated with Brolucizumab in our clinic, we report one case of conjunctivitis associated with mild anterior uveitis in one male patient who was successfully treated with steroid drops for three weeks, leading to complete resolution. The patient was then switched to another anti-VEGF drug.

This real-life study has several limitations: it was retrospective, was performed on a relatively small cohort of patients who presented different baseline characteristics

and had a follow-up of only 1 year. However, we believe that these data could provide useful information on the use of Brolucizumab combined with a T&E regimen in a real-world setting. In this study, aware of the benefits and potential risks related to the use of Brolucizumab, we adopted a T&E regimen to reach the highest IV injection interval, reducing the number of treatments and the possible risk of adverse events as much as possible, with promising functional and structural results.

Conclusions

In conclusion, Brolucizumab IV injections were effective for the treatment of both naïve and previously treated patients, with significantly greater anatomical and functional results in the naïve cohort. In the naïve cohort, 55% of the patients achieved a q12w fluid-free regimen at the end of the follow-up.

Acknowledgements
not applicable.

Author contributions
All the authors contributed to the study conception and design.Material preparation, data collection and analysis were performed by FF, CAL, MN, DB, RK and CR. The first draft of the manuscript was written by FF, CAL and MCS. Conception and supervision were performed by FF, SR, DB and FG. All the authors have read and approved the final manuscript.

Funding
No funds, grants or other support was received to assist with the conceptualization, preparation or writing of this manuscript.

Data availability
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study, conducted in the Ophthalmology Department, ASL TO5, Turin, Italy, was approved by the Local Ethics Committee (protocol number 155/2020, general registry number n°11486, Inter-Hospital Ethics Committee, San Luigi Gonzaga Hospital, Orbassano, Italy) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

Consent for publication
For personal data (i.e., imaging), consent for publication was obtained from all subjects.

Competing interests
The authors declare no competing interests.

Author details
[1]Ophthalmology Unit, Surgical Department, A.O. Ordine Mauriziano, Turin, Italy
[2]Ophthalmology Unit, Surgical Department, ASL TO5, Chieri, Italy
[3]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[5]Ophthalmic Unit, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy
[6]Ophthalmology Unit, Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy
[7]Catholic University "Sacro Cuore", Rome, Italy
[8]Italian National Research Council, CNR, Pisa, Italy
[9]Vitreoretinal Surgery Unit, "Fatebenefratelli Isola Tiberina – Gemelli Isola" Hospital, Rome, Italy
[10]Neuromuscular and Sense Organs Department, Eye Clinic, Careggi University Hospital, Florence, Italy
[11]Department of Neurosciences, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

Received: 10 March 2024 / Accepted: 30 September 2024
Published online: 04 October 2024

References

1. Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng C-Y, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Global Health. 2014. https://doi.org/10.1016/S2214-109X(13)70145-1.
2. Baumal CR. Wet age-related macular degeneration: treatment advances to reduce the injection burden. Am J Manag Care. 2020;26(5 Suppl):S103–11. https://doi.org/10.37765/ajmc.2020.43435.
3. Heier JS, Brown DM, Chong V, Korobelnik J-F, Kaiser PK, Nguyen QD, et al. Intravitreal Aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012. https://doi.org/10.1016/j.ophtha.2012.09.006.
4. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006. https://doi.org/10.1056/NEJMoa054481.
5. CATT Research Group, Martin DF, Maguire MG, Ying G, Grunwald JE, Fine SL, et al. Ranibizumab and Bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011. https://doi.org/10.1056/NEJMoa1102673.
6. Rosenberg D, Deonarain DM, Gould J, Sothivannan A, Phillips MR, Sarohia GS, et al. Efficacy, safety, and treatment burden of treat-and-extend versus alternative anti-VEGF regimens for nAMD: a systematic review and meta-analysis. Eye (Lond). 2023. https://doi.org/10.1038/s41433-022-02020-7.
7. Kertes PJ, Galic IJ, Greve M, Williams RG, Rampakakis E, Scarino A, et al. Canadian Treat-and-Extend Analysis Trial with Ranibizumab in patients with neovascular age-related Macular Disease. Ophthalmology. 2019. https://doi.org/10.1016/j.ophtha.2019.01.013.
8. Heier JS, Khanani AM, Quezada Ruiz C, Basu K, Ferrone PJ, Brittain C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet. 2022. https://doi.org/10.1016/S0140-6736(22)00010-1.
9. Dugel PU, Koh A, Ogura Y, Jaffe GJ, Schmidt-Erfurth U, Brown DM, et al. HAWK and HARRIER: phase 3, Multicenter, Randomized, double-masked trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2020. https://doi.org/10.1016/j.ophtha.2019.04.017.
10. Hsu AY, Lin C-Y, Lin C-J, Lai C-T, Hsia N-Y, Lin J-M et al. Short-Term Effects of Brolucizumab in the Treatment of Wet Age-Related Macular Degeneration or Polypoidal Choroidopathy Refractory to Previous Anti-Vascular Endothelial Growth Factor Therapy. Medicina (Kaunas). 2022; https://doi.org/10.3390/medicina58121703
11. Nam SW, Byun Z, Ham D-I, Kong M. Response to brolucizumab treatment for refractory serous pigment epithelial detachment secondary to polypoidal choroidal vasculopathy. BMC Ophthalmol. 2022. https://doi.org/10.1186/s12886-022-02711-5.
12. Gigon A, Vadalà M, Bonfiglio VME, Reibaldi M, Eandi CM. Early OCTA Changes of Type 3 Macular Neovascularization Following Brolucizumab Intravitreal Injections. Med (Kaunas). 2022. https://doi.org/10.3390/medicina58091180.
13. Matsumoto H, Hoshino J, Mukai R, Nakamura K, Akiyama H. One-year results of treat-and-extend regimen with intravitreal brolucizumab for treatment-naïve neovascular age-related macular degeneration with type 1 macular neovascularization. Sci Rep. 2022. https://doi.org/10.1038/s41598-022-10578-1.
14. Scupola A, Carlà MM, Boselli F, Giannuzzi F, De Filippis A, Fossataro C, et al. Brolucizumab for Wet Age-Related Macular Degeneration: one-year real-world experience from a Tertiary Center. Ophthalmologica. 2023. https://doi.org/10.1159/000529817.
15. Monés J, Srivastava SK, Jaffe GJ, Tadayoni R, Albini TA, Kaiser PK, et al. Risk of inflammation, retinal vasculitis, and retinal occlusion–related events with Brolucizumab. Ophthalmology. 2021. https://doi.org/10.1016/j.ophtha.2020.11.011.

16. Khanani AM, Zarbin MA, Barakat MR, Albini TA, Kaiser PK. Safety outcomes of Brolucizumab in Neovascular Age-Related Macular Degeneration: results from the IRIS Registry and Komodo Healthcare Map. JAMA Ophthalmol. 2022. https://doi.org/10.1001/jamaophthalmol.2021.4585.
17. Ohji M, Takahashi K, Okada AA, Kobayashi M, Matsuda Y, Terano Y, et al. Efficacy and safety of Intravitreal Aflibercept treat-and-extend regimens in Exudative Age-Related Macular Degeneration: 52- and 96-Week findings from ALTAIR: a Randomized Controlled Trial. Adv Ther. 2020. https://doi.org/10.1007/s12325-020-01236-x.
18. Gillies MC, Hunyor AP, Arnold JJ, Guymer RH, Wolf S, Pecheur FL, et al. Macular Atrophy in Neovascular Age-Related Macular Degeneration: a randomized clinical trial comparing Ranibizumab and Aflibercept (RIVAL Study). Ophthalmology. 2020. https://doi.org/10.1016/j.ophtha.2019.08.023.
19. Ohji M, Okada AA, Sasaki K, Moon SC, Machewitz T, Takahashi K, et al. Relationship between retinal fluid and visual acuity in patients with exudative age-related macular degeneration treated with intravitreal aflibercept using a treat-and-extend regimen: subgroup and post-hoc analyses from the ALTAIR study. Graefes Arch Clin Exp Ophthalmol. 2021. https://doi.org/10.1007/s00417-021-05293-y.
20. Simader C, Ritter M, Bolz M, Deák GG, Mayr-Sponer U, Golbaz I, et al. Morphologic parameters relevant for visual outcome during anti-angiogenic therapy of neovascular age-related macular degeneration. Ophthalmology. 2014;1. https://doi.org/10.1016/j.ophtha.2013.12.029.
21. Haji H, Gianniou C, Brynskov T, Sørensen TL, Olsen R, Krogh Nielsen M. Association between structural and functional treatment outcomes in neovascular age-related macular degeneration. Acta Ophthalmol. 2023. https://doi.org/10.1111/aos.15233.
22. Evans RN, Reeves BC, Maguire MG, Martin DF, Muldrew A, Peto T, et al. Associations of Variation in Retinal Thickness with Visual Acuity and anatomic outcomes in eyes with Neovascular Age-Related Macular Degeneration lesions treated with anti-vascular endothelial growth factor agents. JAMA Ophthalmol. 2020. https://doi.org/10.1001/jamaophthalmol.2020.3001.
23. Chakravarthy U, Havilio M, Syntosi A, Pillai N, Wilkes E, Benyamini G, et al. Impact of macular fluid volume fluctuations on visual acuity during anti-VEGF therapy in eyes with nAMD. Eye (Lond). 2021. https://doi.org/10.1038/s41433-020-01354-4.
24. Gianniou C, Dirani A, Jang L, Mantel I. Refractory intraretinal or subretinal fluid in neovascular age-related macular degeneration treated with intravitreal ranizubimab: functional and structural outcome. Retina. 2015. https://doi.org/10.1097/IAE.0000000000000465.
25. Lai T-T, Hsieh Y-T, Yang C-M, Ho T-C, Yang C-H. Biomarkers of optical coherence tomography in evaluating the treatment outcomes of neovascular age-related macular degeneration: a real-world study. Sci Rep. 2019. https://doi.org/10.1038/s41598-018-36704-6.
26. Guymer RH, Markey CM, McAllister IL, Gillies MC, Hunyor AP, Arnold JJ, et al. Tolerating Subretinal Fluid in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab using a treat-and-extend regimen. Ophthalmology. 2019. https://doi.org/10.1016/j.ophtha.2018.11.025.
27. Waldstein SM, Simader C, Staurenghi G, Chong NV, Mitchell P, Jaffe GJ, et al. Morphology and visual acuity in Aflibercept and Ranibizumab Therapy for Neovascular Age-Related Macular Degeneration in the VIEW trials. Ophthalmology. 2016. https://doi.org/10.1016/j.ophtha.2016.03.037.
28. Dugel PU, Singh RP, Koh A, Ogura Y, Weissgerber G, Gedif K et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of Brolucizumab for Neovascular Age-Related Macular Degeneration Ophthalmology. 2021; https://doi.org/10.1016/j.ophtha.2020.06.028
29. Lally DR, Loewenstein A, Arnold JJ, Yang YC, Gedif K, Best C, et al. Efficacy and safety of brolucizumab versus aflibercept in eyes with early persistent retinal fluid: 96-week outcomes from the HAWK and HARRIER studies. Eye (Lond). 2023. https://doi.org/10.1038/s41433-022-02092-5.
30. Matsumoto H, Hoshino J, Nakamura K, Akiyama H. Two-year outcomes of treat-and-extend regimen with intravitreal brolucizumab for treatment-naïve neovascular age-related macular degeneration with type 1 macular neovascularization. Sci Rep. 2023. https://doi.org/10.1038/s41598-023-30146-5.
31. Abdin AD, Aljundi W, El Jawhari K, Suffo S, Weinstein I, Seitz B. First Year Real Life Experience with Intravitreal Brolucizumab for Treatment of Refractory Neovascular Age-Related Macular Degeneration. Front Pharmacol. 2022. https://doi.org/10.3389/fphar.2022.860784.
32. MacCumber MW, Wykoff CC, Karcher H, Adiguzel E, Sinha SB, Vishwakarma S, et al. One-year brolucizumab outcomes in Neovascular Age-Related Macular Degeneration from a large United States Cohort in the IRIS® Registry. Ophthalmology. 2023. https://doi.org/10.1016/j.ophtha.2023.04.012.
33. Holz FG, Iida T, Maruko I, Sadda SR. A consensus on risk mitigation for brolucizumab in neovascular age-related macular degeneration. Retina. 2022. https://doi.org/10.1097/IAE.0000000000003556.
34. Baumal CR, Bodaghi B, Singer M, Tanzer DJ, Seres A, Joshi MR, et al. Expert Opinion on Management of intraocular inflammation, retinal vasculitis, and vascular occlusion after Brolucizumab Treatment. Ophthalmol Retina. 2021. https://doi.org/10.1016/j.oret.2020.09.020.
35. Fonollosa A, Gallego-Pinazo R, Sararols L, Adán A, López-Gálvez M, Figueroa MS. Guidance on brolucizumab management recommendations. Arch Soc Esp Oftalmol (Engl Ed). 2022. https://doi.org/10.1016/j.oftale.2022.05.006.
36. Mora P, Bellucci C, Radice LM, Manzotti F, Gandolfi S. Changes in the uninjected contralateral eye after intravitreal brolucizumab for exudative age-related macular degeneration. Eur J Ophthalmol. 2024. https://doi.org/10.1177/11206721231187429.

Publisher's note